REMARKS

Reconsideration of this application is respectfully requested.

Status of the Claims

In response to a Restriction Requirement, claims 1-3, 5, 6, and 13 were elected for prosecution on the merits. Claims 4 and 7-12 have been withdrawn from consideration. Therefore, only claims 1-3, 5, 6, and 13 are at issue.

Claim 14 has been added to specifically recite Compound 37 disclosed in the Specification. No new matter has been added to the application.

Upon entry of this Amendment, claims 1-14 are pending.

Objection to the Claims

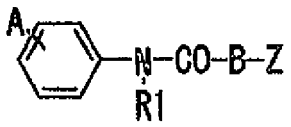
Claim 1 has been objected to because Formula 1 is not shown. Formula 1, present in claim 1 of the originally filed application, was inadvertently omitted in the listing of claims presented in the Preliminary Amendment dated October 12, 2005, which did not amend claim 1. The above listing of claims correctly depicts Formula 1 as found in original claim 1. Thus, the basis for the objection has been addressed, and it is respectfully requested that it be withdrawn.

Claim Rejection under 35 U.S.C. § 103

Claims 1-3, 5, 6, and 13 have been rejected under 35 U.S.C. § 103(a) as obvious over Umeda et al. (U.S. Patent No. 6,342,516; "the '516 patent") in view of Hansch et al. (Substituent Constants for Correlation Analysis in Chemistry and Biology (1979), pages 1-63). According to the Examiner, the '516 patent teaches an anti-oxidant compound that is structurally similar to the elected species of the present invention, differing in that it substitutes an acetate group for the amino group on the benzofuran ring. The Examiner's position is that it would have been obvious to make this substitution in view of a quantitative structure-activity relatationship described by Hansch et al.

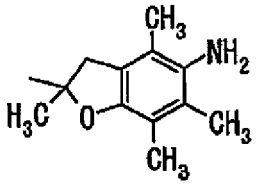
Applicants respectfully disagree and request reconsideration for the following reasons.

Compound 37 of the present invention is represented by the formula (1):



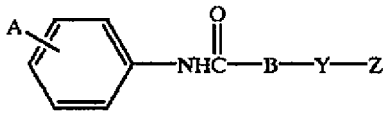
(1)

wherein Z is a group represented by the following formula:



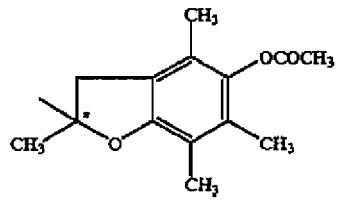
In the Specification, Applicants demonstrated that such a chemical structure results in excellent tissue migration, which contributes to passing it easily through the blood-brain barrier or blood-retina barrier, and exhibits excellent *in vivo* antioxidative action regardless of the route of administration. *See* Specification, pages 65-70 (Examples 4-6).

In contrast, the '516 patent discloses Compound 3-19 represented by the following formula (A):



(A)

wherein A represents 4-1H-pyrazol-5-yl, B and Y each represents a single bond, and Z represents a group represented by the following formula:

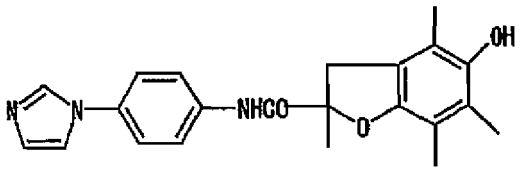


However, the '516 patent does not teach or suggest that the -$OCOCH_3$ group on the 2,3-dihydrobenzofuran ring should be substituted with an -NHR group (wherein R represents a hydrogen atom, a C1-6 alkylcarbonyl group, or an optionally substituted benzoyl group).

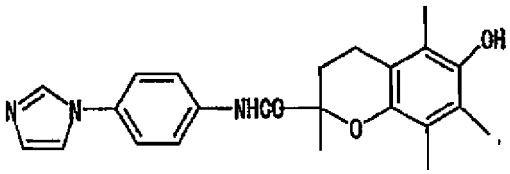
The Examiner contends that "one of ordinary skill in the art would have found it obvious to make a substitution of –NH2 on compound 3-19 in the '516 patent and arrive at the instant invention based on the QSAR [quantitative structure-activity relationship] methodology well-known in the art and exemplified by Hansch et al." Office Action at page 5. However, the QSAR methodology, and Hansch et al. in particular, does not teach that the two substituents are interchangeable or suggest that they are related in any way that would motivate the skilled artisan to choose the particular substitution from among the many possibilities. The methodology is merely an invitation to experiment, which attempts to minimize the amount of trial-and-error involved in optimizing drug targets. *See* Hansch et al., page 48. Neither the '516 patent nor Hansch et al. teaches or suggests that modifying the prior art as proposed by the Examiner would yield predictable results.

Furthermore, the combined teachings of the '516 patent and the QSAR methodology, as exemplified by Hansch et al., fail to disclose or suggest that substituting -$OCOCH_3$ on the 2,3-dihydrobenzofuran-2-yl group in formula (A) with an -NHR group, such as –NH2, would achieve the superior and unexpected effects exhibited by Compound 37, as discussed below.

In Example 5 of the Specification, it has been demonstrated that Compound 37 exhibited significantly higher antioxidative action *in vivo* than that of Control drugs 1 and 2, which are disclosed in the '516 patent. Control drugs 1 and 2 are represented by the following formulas:



Control drug 1



Control drug 2

The antioxidative effects of Compound 37 and Control drugs 1 and 2 were evaluated *in vivo* based on the inhibitory effects on abnormal behavior and mortality (using the method of J. Med. Chem. 1997, 40:559-573). The test compounds were dissolved or suspended in a saline solution and administered to mice 30 minutes before the administration of ferrous chloride. The 50% inhibitory dose was determined from scores of each compound and a control group. As demonstrated in the results tabulated in Table 5, Compound 37 exhibited significantly higher antioxidative action *in vivo* than that of Control drugs 1 and 2.

Because Control drugs 1 and 2 exhibited increased antioxidative action *in vitro* when compared to Compound 37 (*see* Example 3 of the Specification), it is apparent that Control drugs 1 and 2 could not easily pass through the blood-brain barrier to migrate into the central nervous system, and therefore they could not exhibit sufficient antioxidative action *in vivo* at a small dose. In contrast, since Compound 37 exhibited excellent antioxidative action both *in vitro* and *in vivo*, even at a small dose, it is apparent that Compound 37 could easily pass through the blood-brain barrier to migrate into the central nervous system.

Moreover, in the attached declaration co-inventor Seiichi Uchida compared the antioxidative action of Compound 37 and Compound 3-19 disclosed in the '516 patent. Each compound was dissolved in DMSO and suspended in a saline solution, which was administered to male SD rats. The lipid peroxide activity of brain tissue was measured as described in Example 3 of the Specification, and inhibition rates were determined from the amount of lipid peroxide formed when compared to a control group.

Compound 3-19 did not exhibit any anti-lipid peroxide action, even at a high dose, demonstrating that it did not pass through the blood-brain barrier to migrate into the brain. In

contrast, Compound 37 exhibited high anti-lipid peroxide action in the brain, even at a small dose, indicating that it easily passed through the blood-brain barrier.

Thus, unexpected and superior results are realized by the -NHR group of the group Z in formula (1) of the present invention (for example, NH_2 in 2,3-dihydrobenzofuran-2-yl of Compound 37). These results were not expected from the disclosures or teachings of the '516 patent and Hansch et al., neither of which discloses or teaches that the group Z in the formula (A) should be substituted with an -NHR group.

As discussed above, the combined teachings of the '516 patent and Hansch et al. fail to teach or suggest that making the substitution proposed by the Examiner would yield predictable results. In fact, Applicants have demonstrated that superior and unexpected results were realized by the present invention. Accordingly, claims 1-3, 5, 6, and 13 are not obvious over the '516 patent in view of Hansch et al. Withdrawal of the rejection is respectfully requested.

New Claims

New claim 14 specifically recites Compound 37 disclosed in the Specification. Claim 14 depends from claim 1, and is allowable for at least the reasons discussed above.

CONCLUSION

In view of the above amendments and remarks, all of the rejections and objections have been overcome, and the allowance of claims 1-3, 5, 6, and 13 is respectfully requested. If there are any remaining issues that the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

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Respectfully submitted,

By _____

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